

# Early initiation of direct anticoagulation after stroke in patients with atrial fibrillation

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**Background and purpose:** The safety of early initiation of anticoagulant therapy in patients with ischaemic stroke related to atrial fibrillation (AF) is unknown. We investigated the safety of early initiation of direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs) or no anticoagulation.

**Methods:** This observational, retrospective, single-centre study included consecutive patients with recent (<4 weeks) ischaemic stroke and AF. The primary outcome was the rate of major (intracranial and extracranial) bleeding in patients on different treatment schemes, i.e. DOACs, VKAs and not anticoagulated. We also investigated the rate of ischaemic cerebrovascular events and mortality.

**Results:** We included 959 consecutive patients with AF and ischaemic stroke followed up for an average of 16.1 days after the index event. A total of 559 out of 959 patients (58.3%) were anticoagulated with either VKAs ( $n = 259$ ) or DOACs ( $n = 300$ ). Anticoagulation was started after a mean of  $7 \pm 9.4$  days in the DOAC group and  $11.9 \pm 19.7$  days in the VKA group. Early initiation of any anticoagulant was not associated with an increased risk of any major bleeding [odds ratio (OR), 0.49; 95% confidence intervals (CI), 0.21–1.16] and in particular of intracranial bleeding (OR, 0.47; 95% CI, 0.17–1.29;  $P = 0.143$ ) compared with no anticoagulation. In contrast to VKAs (OR, 0.78; 95% CI, 0.28–2.13), treatment with DOACs (OR, 0.32; 95% CI, 0.10–0.96) reduced the rate of major bleeding compared with no anticoagulation. Early recurrences of ischaemic stroke did not differ significantly among the three groups.

**Conclusions:** Starting DOACs within a mean of 7 days after stroke appeared to be safe. Randomized controlled studies are needed to establish the added efficacy of starting anticoagulation early after stroke.

## Introduction

Anticoagulation in stroke patients with atrial fibrillation (AF) is the most effective secondary stroke preventive therapy [1]. Several trials have yielded strong evidence that vitamin K antagonists (VKAs) are much more effective than antiplatelet agents [2]

and the direct oral anticoagulants (DOACs) Dabigatran, Apixaban, Rivaroxaban and Edoxaban are at least as effective as VKAs for stroke prevention in AF [3–6].

In the above-mentioned trials, the latency between the stroke and the earliest initiation of a DOAC varied between 7 and 30 days after the event. The main reason for this protocol restriction was concern about secondary haemorrhage into the infarct in the acute phase of ischaemic stroke. In clinical practice, it is desirable to start anticoagulation as soon as possible after the event because the risk of recurrence is

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highest in the acute phase [7,8]. Moreover, adherence is better if prevention is started in inpatients shortly after the event [9,10].

Interdisciplinary expert opinion of the European Heart and Rhythm Association recommends starting DOACs with a 1–12-day delay after stroke or transient ischaemic attack (TIA) depending on the infarct size [11]. A recent review by Paciaroni *et al.* [12] suggested that the best timing for initiating anticoagulant treatment for secondary stroke prevention is between 4 and 14 days from stroke onset. However, the evidence supporting this recommendation is limited.

In this study, we investigated the safety of early initiation of DOACs and VKAs compared with no anticoagulation in patients with AF after an ischaemic stroke. We also investigated the rate of early recurrence of ischaemic cerebrovascular events and mortality in stroke patients with AF on different treatment schemes early after the event.

## Methods and materials

The early initiation of direct anticoagulation after stroke in patients with atrial fibrillation (EIDASAF) study was an investigator-initiated, observational, retrospective single-centre study. The study considered enrolment of all acute ischaemic stroke patients who were treated at the Hyper Acute Stroke Unit of the Imperial College Healthcare NHS Trust between 2010 and 2017.

The EIDASAF study was approved by the Health Research Authority for collection of data within the NHS. The research did not require review by the UK Health Departments Research Ethics Service as it fell into the category of 'Research limited to use of previously collected, non-identifiable information.' Informed consent was not a legal requirement as the research was carried out using data collected as part of routine care and any researchers outside the direct care team only had access to anonymized data.

The following eligibility criteria had to be fulfilled: (i) age  $\geq 18$  years; (ii) recent ( $<4$  weeks) ischaemic stroke and (iii) documentation of AF before or early after the index stroke. Exclusion criteria were (i) another primary reason for anticoagulation and intracranial haemorrhage or (ii) major systemic haemorrhage after the index event that occurred before initiating oral anticoagulant.

## Data source and data collection process

Consecutive enrolment of eligible patients was ensured by using a database of admissions that is used for

reporting to a central UK stroke data bank (Sentinel Stroke National Audit Programme). Electronic and paper-based medical records of eligible patients were retrieved from the Imperial College Healthcare NHS Trust medical archive. Data of consecutive patients were extracted using a pre-specified case report file that encompassed patient characteristics, including age, vascular risk factors, laboratory results, relevant medical history and medications including the start of the anticoagulant treatment, that were recorded during the admission. Events were captured by review of medical notes of all patients admitted to the Hyper Acute Stroke Unit of the Imperial College Healthcare NHS Trust between 2010 and 2017. The severity of the index stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS) score on admission. Choice of anticoagulant and timing of initiation of anticoagulant were made by the treating physicians. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score [13] for estimating the risk of stroke in patients with AF was calculated based on available records.

## Image analysis

Cranial computed tomography without contrast or brain magnetic resonance imaging was performed on admission in all patients as part of routine clinical care to exclude intracranial haemorrhage. The images were inspected by experienced stroke researchers to identify the causative acute ischaemic lesion(s). This lesion was delineated manually using MRICroN software (version 12/2009; C. Rordens [14]) in native space to obtain the volume. Mature lesions and leukoaraiosis were excluded.

## Definition of study variables

The main study outcome variables (major bleeding, recurrent cerebrovascular events and death) were identified by a careful search of each medical record, including the discharge diagnosis, by trained stroke physicians.

The primary outcome was major bleeding, which was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells [15].

The brain scans were inspected by neuroradiologists and/or experienced stroke researchers to define the intracranial haemorrhage type [16]. Haemorrhagic

infarction (HI) was defined as small petechiae along the margins of the infarct (HI-1) or as more confluent petechiae within the infarcted area but without space-occupying effect (HI-2). Parenchymal haematoma (PH) was defined as haematoma in <30% of the infarcted area with some slight space-occupying effect (PH-1) or as dense haematoma in  $\geq 30\%$  of the infarcted area with substantial space-occupying effect or as any haemorrhagic lesion outside the infarcted area (PH-2). In case of more than one haemorrhagic lesion on brain scan, the worst possible category was assumed. In addition, intracranial bleeding included any local or remote parenchymal haemorrhage, subdural and subarachnoid haemorrhages combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS score between baseline and 24 h, or leading to death, in the absence of any bleeding evidence on the first computed tomography [16,17].

Ischaemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction [18]. High blood pressure was defined as blood pressure of  $\geq 140/90$  mmHg at least twice before stroke or already under treatment with antihypertensive drugs. Diabetes mellitus was defined as history of diabetes that was confirmed in medical records and/or fasting glucose level  $\geq 126$  mg/dL preprandial on two examinations, glucose level  $\geq 200$  mg/dL post-prandial or HbA1c  $\geq 6.5\%$ , or under antidiabetic treatment.

The following data on known stroke risk factors were collected: current cigarette smoking, past smoking (cessation < 5 years ago), hyperlipidaemia (total cholesterol  $\geq 200$  mg/dL or triglyceride  $\geq 140$  mg/dL or already on lipid-lowering therapy), history of symptomatic ischaemic heart disease (myocardial infarction, history of angina or existence of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent claudication of presumed atherosclerotic origin; ankle/arm systolic blood pressure ratio < 0.85 in either leg at rest; history of intermittent claudication with previous leg amputation, reconstructive surgery or angioplasty) or previous ischaemic stroke/TIA or intracranial haemorrhage.

Data on the use of any antiplatelet agents or anticoagulants before admission, at baseline and during the admission period were recorded. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score (2 points for a history of stroke or age  $\geq 75$  years and 1 point each for age 65–74 years, history of hypertension, diabetes, cardiac failure, sex category female and vascular disease) after the index event was also calculated [13].

## Statistical analysis

Sample characteristics are presented as absolute and relative (%) frequencies for categorical variables and as median and interquartile range or mean and SD for continuous variables as appropriate. Comparisons among the three groups of patients (not treated with anticoagulants, treated with DOACs and treated with VKAs) were conducted by chi-squared tests for categorical variables or one-way ANOVA for continuous variables as appropriate.

We fitted separate multivariable logistic regression models to assess the association between receiving any anticoagulant (versus not treated with anticoagulants) for each of the primary outcomes of major bleeding. Independent variables in each of these models also included age, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, NIHSS score (as continuous variable) and lesion volume. Similar logistic regression models were also fitted to compare treatment with DOACs versus no anticoagulant and treatment with VKAs versus no anticoagulant. The final specification of all regression models was decided through an iterative process based on likelihood ratio tests; when two models showed similar fit to our data, we selected the most parsimonious one. Results are presented as odds ratios (ORs) with 95% confidence intervals (CI). We also present *P*-values with significance level set at 0.05. All analyses were conducted with Stata 15 (StataCorp LLC, College station, TX, USA).

## Results

### Baseline data and demographics

Overall, 959 consecutive patients with AF and ischaemic stroke were included in the study and were followed up in-hospital with an average of 16.1 days. The clinical characteristics are listed in Table 1. After the index event, 559 out of 959 patients (58.3%) were treated with anticoagulants. A total of 300 patients (31.3%) received DOACs and 259 patients (27.0%) received warfarin; 43 patients out of 259 patients (16.6%) received Low-molecular-weight heparin (LMWH) followed by VKAs.

A total of 239 patients (74.7%) were treated with Apixaban, 45 (13.5%) with Rivaroxaban, 13 (4.2%) with Dabigatran and 3 (1.0%) with Edoxaban.

The clinical characteristics of the patients treated with DOACs, VKA or no anticoagulation are listed in Table 1. Non-anticoagulated patients were more frequently female ( $P = 0.006$ ) and had a higher percentage of previous intracranial haemorrhage ( $P = 0.009$ ) and previously known AF ( $P < 0.001$ ). They also had a more severe stroke based on higher NIHSS admission score

**Table 1** Clinical characteristics of the patients

|                                        | All patients ( <i>n</i> = 959) | DOACs<br>( <i>n</i> = 300) | VKAs<br>( <i>n</i> = 259) | Not treated<br>( <i>n</i> = 388) | <i>P</i> -value |
|----------------------------------------|--------------------------------|----------------------------|---------------------------|----------------------------------|-----------------|
| Age (years)                            | 80 (73–86)                     | 80 (73–85)                 | 78<br>(72–83)             | 82<br>(75–88)                    | 0.236           |
| Male                                   | 483 (50.4)                     | 162 (54)                   | 144 (55.6)                | 172<br>(44.3)                    | 0.006           |
| Smoking                                | 80<br>(8.3)                    | 25 (10.6)                  | 25 (12.3)                 | 29<br>(9.0)                      | 0.080           |
| Hypertension                           | 721<br>(75.2)                  | 218 (72.7)                 | 201 (77.6)                | 292<br>(75.3)                    | 0.402           |
| Diabetes                               | 219<br>(22.8)                  | 64<br>(21.3)               | 66 (25.5)                 | 86<br>(22.2)                     | 0.469           |
| Hypercholesterolaemia                  | 480<br>(50.1)                  | 149 (49.7)                 | 147 (56.8)                | 179<br>(46.1)                    | 0.029           |
| Coronary artery disease                | 269 (28.1)                     | 65 (21.7)                  | 84 (32.4)                 | 112 (28.9)                       | 0.013           |
| Heart failure                          | 116 (12.1)                     | 32 (10.7)                  | 36 (13.9)                 | 48 (12.4)                        | 0.506           |
| Peripheral vascular disease            | 77 (8.0)                       | 28 (9.3)                   | 21 (8.1)                  | 26 (6.7)                         | 0.444           |
| Previous TIA                           | 127 (13.2)                     | 34 (11.3)                  | 41 (15.8)                 | 51 (13.1)                        | 0.294           |
| Previous ICH                           | 12 (1.3)                       | 2 (0.7)                    | —                         | 10 (2.6)                         | 0.009           |
| Previously known AF                    | 764<br>(79.7)                  | 233<br>(77.7)              | 185 (71.4)                | 337 (87.1)                       | < 0.001         |
| NIHSS score on admission               | 6 (2–13)                       | 3 (2–8)                    | 4 (2–9)                   | 11 (4–19)                        | <0.001          |
| NIHSS score $\geq 10$                  | 299<br>(31.18)                 | 57 (19.3)                  | 49 (24.6)                 | 193<br>(55.3)                    | <0.001          |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc | 6 (5–6)                        | 5 (4–6)                    | 5 (5–6)                   | 6 (3–12)                         | 0.003           |
| Thrombolysis                           | 146<br>(15.22)                 | 50 (16.72)                 | 34 (13.33)                | 62 (16.32)                       | 0.490           |
| Lesion volume (mL)                     | 6.3 (1.06–26.79)               | 3.59 (0.64–13.91)          | 3.87 (0.67–15.13)         | 13.75 (2.52–53.67)               | < 0.001         |

AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack; VKA, vitamin K antagonist. Data are given as median (interquartile range) and *n* (%).

( $P < 0.001$ ), higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $P = 0.003$ ) and a larger stroke lesion volume ( $P < 0.001$ ).

The cohort of patients treated with any VKA had more hypercholesterolaemia ( $P = 0.029$ ) and coronary artery disease ( $P = 0.013$ ) compared with patients treated with DOACs and non-anticoagulated patients.

### Timing of initiation of anticoagulation

Anticoagulant treatment was initiated after a mean of  $9.2 \pm 14.9$  days after the index event. There was no statistically significant difference between the mean time of starting DOACs ( $7 \pm 9.4$  days) and VKAs ( $11.9 \pm 19.7$  days) ( $P = 0.182$ ).

### Primary outcome

The rate of any major bleeding was 3% in patients treated with any anticoagulant compared with 4.4% in the non-anticoagulated group ( $P = 0.276$ ) (Table 2). The rate of major extracranial bleeding was 1.2% in anticoagulated patients versus 0.5% in non-anticoagulated patients ( $P = 0.250$ ). Patients treated with VKAs had a significantly higher rate of any major bleeding and particularly of extracranial

bleeding when compared with patients treated with DOACs or non-anticoagulated patients ( $P = 0.016$  and  $P = 0.028$ , respectively) (Table 2).

**Table 2** Risk of early major bleeding in the groups of patients treated with anticoagulants and not treated with anticoagulants after the acute stroke

|                       | Any anticoagulant<br>( <i>n</i> = 559) | Not treated<br>( <i>n</i> = 388) | <i>P</i> -value |
|-----------------------|----------------------------------------|----------------------------------|-----------------|
| Major bleeding        | 17 (3)                                 | 17 (4.4)                         | 0.276           |
| Intracranial bleeding | 10 (1.8)                               | 15 (3.9)                         | 0.051           |
| Extracranial bleeding | 7 (1.2)                                | 2 (0.5)                          | 0.250           |

  

|                       | DOACs<br>( <i>n</i> = 300) | VKAs<br>( <i>n</i> = 259) | Not treated<br>( <i>n</i> = 388) | <i>P</i> -value |
|-----------------------|----------------------------|---------------------------|----------------------------------|-----------------|
| Major bleeding        | 5 (1.7)                    | 12 (4.6)                  | 17 (4.4)                         | 0.016           |
| Intracranial bleeding | 4 (1.3)                    | 6 (2.3)                   | 15 (3.9)                         | 0.113           |
| Extracranial bleeding | 1 (0.3)                    | 6 (2.3)                   | 2 (0.5)                          | 0.028           |

Intracranial bleeding included any local or remote parenchymal haemorrhage, subdural and subarachnoid haemorrhages combined with a neurological deterioration of  $\geq 4$  points on the National Institutes of Health Stroke Scale (NIHSS) from baseline or from the lowest NIHSS score between baseline and 24 h, or leading to death, in the absence of any bleeding evidence on the first computed tomography (see methods). DOAC, direct oral anticoagulant; VKA, vitamin K antagonist. Data are given as *n* (%).

**Table 3** Early major bleeding outcome

| Variable                                 | OR   | 95% CI    | P-value |
|------------------------------------------|------|-----------|---------|
| Any anticoagulant vs. no anticoagulation | 0.49 | 0.21–1.16 | 0.106   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc   | 0.99 | 0.70–1.40 | 0.983   |
| Age                                      | 1.02 | 0.97–1.07 | 0.381   |
| NIHSS score                              | 0.98 | 0.92–1.04 | 0.599   |
| Lesion volume                            | 0.99 | 0.98–1.00 | 0.343   |
| Any DOACs vs. no anticoagulation         | 0.32 | 0.10–0.96 | 0.043   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc   | 0.85 | 0.56–1.26 | 0.417   |
| Age                                      | 1.03 | 0.97–1.08 | 0.339   |
| NIHSS score                              | 0.99 | 0.93–1.06 | 0.855   |
| Lesion volume                            | 0.99 | 0.98–1.00 | 0.382   |
| VKAs vs. no anticoagulation              | 0.78 | 0.28–2.13 | 0.632   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc   | 0.99 | 0.67–1.46 | 0.978   |
| Age                                      | 1.01 | 0.96–1.07 | 0.615   |
| NIHSS score                              | 0.98 | 0.92–1.04 | 0.601   |
| Lesion volume                            | 0.99 | 0.98–1.00 | 0.313   |

CI, confidence intervals; DOAC, direct oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; VKA, vitamin K antagonist.

Any intracranial bleeding occurred in 1.8% of the anticoagulated patients and in 3.9% of the non-anticoagulated patients ( $P = 0.051$ ). Indeed, 1.3% of patients treated with DOAC experienced an intracranial haemorrhage after the start of the treatment compared with 2.3% in the VKA group ( $P = 0.113$ ).

Table S1 shows the type of intracranial haemorrhages according to the SITS-MOST classification [16] (see methods) in the groups of patients treated with DOAC, VKA or no anticoagulation. In the DOAC group, 0.7% were classified as PH-2 and 0.7% as 3d; in the VKA group 0.8% were PH-1, 1.2% were PH-2 and 0.4% were 3b. Conversely, among the 388 untreated patients who were included in the analysis, 2.9% were classified as PH-1, 0.6% as PH-2 and 0.3% as 3b (Table S1).

We performed multivariable logistic regression analysis to adjust for the imbalances of patient characteristics at baseline (Tables 3 and 4). Initiation of anticoagulation after acute stroke was not associated with an increased risk of any major bleeding compared with no anticoagulation (OR, 0.49; 95% CI, 0.21–1.16;  $P = 0.106$ ). Treatment with any DOAC (OR, 0.32; 95% CI, 0.10–0.96;  $P = 0.043$ ) but not with a VKA (0.78; 95% CI, 0.28–2.13;  $P = 0.632$ ) decreased the odds of major bleeding compared with no anticoagulation (Table 3).

Multivariable logistic regression analysis with the factors associated with intracranial bleeding is shown in Table 4. Initiation of any anticoagulant after acute stroke was not associated with a significantly increased risk of intracranial bleeding compared with

**Table 4** Intracranial bleeding outcome

| Variable                                 | OR   | 95% CI    | P-value |
|------------------------------------------|------|-----------|---------|
| Any anticoagulant vs. no anticoagulation | 0.47 | 0.17–1.29 | 0.143   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc   | 0.90 | 0.60–1.34 | 0.608   |
| Age                                      | 1.03 | 0.98–1.10 | 0.208   |
| NIHSS score                              | 1.02 | 0.96–1.08 | 0.515   |
| Lesion volume                            | 0.99 | 0.98–1.00 | 0.366   |
| Any DOACs vs. no anticoagulation         | 0.23 | 0.60–0.90 | 0.035   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc   | 0.74 | 0.47–1.17 | 0.205   |
| Age                                      | 1.04 | 0.98–1.10 | 0.219   |
| NIHSS score                              | 1.01 | 0.94–1.08 | 0.879   |
| Lesion volume                            | 0.98 | 0.01–3.74 | 0.470   |
| VKAs vs. no anticoagulation              | 0.62 | 0.18–2.12 | 0.446   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc   | 0.86 | 0.54–1.34 | 0.483   |
| Age                                      | 1.04 | 0.97–1.09 | 0.312   |
| NIHSS score                              | 1.01 | 0.94–1.08 | 0.922   |
| Lesion volume                            | 1.00 | 0.99–1.01 | 0.438   |

CI, confidence intervals; DOAC, direct oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; VKA, vitamin K antagonist.

**Table 5** Rate of recurrent stroke and mortality in the groups of patients treated with any anticoagulants and not treated with anticoagulants after the acute stroke

|                      | Any anticoagulant<br>( <i>n</i> = 559) | Not treated<br>( <i>n</i> = 388) | P-value |
|----------------------|----------------------------------------|----------------------------------|---------|
| Recurrent stroke/TIA | 27 (4.8)                               | 15 (3.9)                         | 0.522   |
| Dead                 | 5 (0.9)                                | 67 (17.3)                        | <0.001  |

  

|                      | DOACs<br>( <i>n</i> = 300) | VKAs<br>( <i>n</i> = 259) | Not treated<br>( <i>n</i> = 388) | P-value |
|----------------------|----------------------------|---------------------------|----------------------------------|---------|
| Recurrent stroke/TIA | 15 (5)                     | 12 (4.6)                  | 15 (3.9)                         | 0.761   |
| Dead                 | 4 (1.3)                    | 1 (0.4)                   | 67 (17.3)                        | <0.001  |

DOAC, direct oral anticoagulant; TIA, transient ischaemic attack; VKA, vitamin K antagonist. Data are given as *n* (%).

no anticoagulation (OR, 0.47; 95% CI, 0.17–1.29;  $P = 0.143$ ). Treatment with any DOACs showed a decreased risk of intracranial bleeding compared with no anticoagulation (OR, 0.23; 95% CI, 0.60–0.90;  $P = 0.035$ ), whereas no effect was found for treatment with VKA versus no anticoagulation (0.62; 95% CI, 0.18–2.12;  $P = 0.446$ ) (Table 4).

#### Recurrent ischaemic stroke and transient ischaemic attack and mortality outcome

The risk of recurrent stroke or TIA during the inpatient stay did not differ significantly between the cohorts of anticoagulated versus non-anticoagulated patients ( $P = 0.522$ ) (Table 5). The risk of death was significantly higher in non-anticoagulated patients ( $P < 0.001$ ).

The rate of recurrent stroke or TIA did not differ among the three groups (ANOVA;  $P = 0.761$ ). Overall, 1.3% of the patients who received any DOACs and 0.4% of the patients treated with VKAs died. In contrast, 17.3% of the group of patients who had not received anticoagulants died ( $P < 0.001$ ) (Table 5). We documented only four out of 959 (0.42%) extra-neurological ischaemic events. These were all pulmonary embolism, which occurred only in the group of non-anticoagulated patients.

## Discussion

The major new finding of our study is that initiation of DOACs early after stroke is safe in terms of intracranial and extracranial bleeding.

Although there are promising results from several multi-centre, observational, non-randomized studies [7,8,19–21] of anticoagulant treatment early after onset of stroke, there are only limited safety data related to early anticoagulation after stroke. Four single-centre observational studies [22–25] reported low frequency of symptomatic intracranial haemorrhage in patients with mild to moderate stroke or small- to medium-sized infarcts with early start of DOAC. In contrast to our study, patients with severe stroke were excluded. Our data provide the largest available single-centre dataset of best-practice stroke-unit patients with AF and a recent cerebral infarct to date.

Starting anticoagulation early after stroke was not associated with an increased rate of intracranial bleeding, which is the most feared complication of the antithrombotic therapy in patients with ischaemic stroke [26]. The lack of excess bleeding resulting from anticoagulation prevailed after adjusting for stroke severity, age, CHA<sub>2</sub>DS<sub>2</sub>-VASc score and lesion size.

We observed important differences between the types of anticoagulant. Although anticoagulation with VKA was started almost 5 days later than DOACs, patients treated with VKAs had a significantly higher risk of early major extracranial haemorrhage compared with patients receiving DOACs or no anticoagulant. This is remarkable because the anticoagulatory effects of DOACs start within hours after taking DOACs, whereas VKAs induce effective anticoagulation after a delay of days. In randomized clinical trials, all DOACs had a reduced risk for intracranial haemorrhage compared with VKAs, whereas the risk of extracranial bleeding varied among the DOAC agents [3–6,27]. It is also noteworthy that 16.6% of our patients treated with VKA received LMWH as bridging therapy. The combined analysis of the RAF and RAF-NOAC data suggested that bridging therapy

was associated with overall higher risks of symptomatic intracranial bleeding compared with patients treated with anticoagulants alone [28].

Our study has several limitations. The retrospective, non-randomized design is likely to have introduced biases. The reported associations in our non-randomized study could be influenced by numerous potential confounders, even if statistical models were used to adjust for them. Specifically, patients who received no anticoagulation had a more severe stroke compared with anticoagulated patients. As infarct volume is a predictor of haemorrhagic transformation after stroke, we caution against early anticoagulation in patients with large ischaemic stroke. Our above-reported associations come from a non-randomized study and, despite the adjustment for important baseline factors, these can be influenced by numerous confounders. However, in several circumstances in which randomized trials are not available, observational studies are considered a useful tool to understand the effects of a treatment or of different clinical services. In addition, if rigorously designed, this type of analysis could help to estimate the effects of interventions, particularly in everyday clinical practice [29]. Despite our efforts, we cannot exclude that our results could have been influenced by an incomplete adjustment for patient characteristics in selecting the model for the multivariable analysis. Unfortunately, we do not have data on potential competing risks for our outcomes. However, due to the relatively short follow-up period, we believe that the impact of competing events has been relatively minimal. We believe that adequately powered randomized trials are required to evaluate the timing for starting oral anticoagulation after an acute stroke [30]. The focus of our study is on clinically apparent intracranial haemorrhages, which are the major concern for starting anticoagulants after ischaemic stroke rather than systemic bleedings. Admittedly, we cannot rule out that clinically silent systemic major bleeding occurred and was not noticed because the treating physicians did not perform routine complete blood counts in all patients. However, 90% of our patients had a follow-up blood test close to their discharge. Finally, for the purpose of this study, we reviewed the Sentinel Stroke National Audit Programme database of admissions and medical records retrieved from the Imperial College Healthcare NHS Trust medical archive. However, although unlikely, we cannot completely exclude the possibility of a limited underassessment, even if we attempted to ascertain almost all of the patient clinical characteristics and risk factors through these multiple overlapping sources.

## Conclusions

The findings of the EIDASAF study suggest that starting anticoagulant treatment with DOACs within the first days after ischaemic stroke is safe in terms of extracranial and intracranial bleeding complications. Randomized controlled studies are needed to establish the added efficacy of starting anticoagulation early after stroke.

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## Disclosure of conflicts of interest

Eleni Korompoki declares speaker honoraria from Amgen, INNOVIS and Pfizer, and advisory boards from Pfizer. Roland Veltkamp has received fees for consulting and speaker honoraria from Bayer, Boehringer Ingelheim, BMS, Pfizer, Daich Sankyo, Portola, Biogen, Medtronic, Morphosys and Amgen as well as research support from Bayer, Boehringer, BMS, Pfizer, Daiichi Sankyo, Medtronic and Biogen outside the present work. The other authors declare no financial or other conflicts of interest.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Description of intracranial haemorrhages in the groups of patients treated with anticoagulants and not treated with anticoagulants after the acute stroke.

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